Phosgene

CAS Number 75-44-5

USEPA HPV Challenge Program Test Plan Submission

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1.0 EXECUTIVE SUMMARY

The member companies of the Phosgene Panel of the American Chemistry Council submit for review and public comment the Test Plan and Robust Summaries for phosgene (Cl_2CO (Fig. 1)) (Chemical Abstract Service (CAS) registry number 75-44-5) under the United States (U.S.) Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. The purpose of this Test Plan is to summarize available physicochemical data, environmental fate and effects, and mammalian health effects data for phosgene consistent with Screening Information Data Set (SIDS) Level 1 endpoints. Table 1 provides a summary of the adequacy of existing data for SIDS Level 1 endpoints and recommended testing for phosgene. Overall, the SIDS data set for phosgene is robust and no further toxicity testing is proposed for SIDS endpoints.

Table 1: Data Summary

Data Point	Data Available	Testing Proposed
Melting Point	Yes	No
Boiling Point	Yes	No
Vapor Pressure	Yes	No
Partition Coefficient	*	No
Water Solubility	*	No
Stability in Water	Yes	No
Transport Between Environmental Compartments	*	No
Photodegradation	Yes	No
Biodegradation	*	No
Acute Toxicity to Fish	*	No
Acute Toxicity to Invertebrates	*	No
Acute toxicity to Aquatic Plants	*	No
Acute Toxicity – Inhalation	Yes	No
Genetic Toxicity *in vivo* – Micronucleus	*	No
Genetic Toxicity *in vitro* – Ames	Yes	No
Repeat dose – inhalation	Yes	No
Reproductive Toxicity	Yes	No
Developmental Toxicity	*	No

* Not an appropriate endpoint because of lack of water stability and reactivity.

2.0 INTRODUCTION

The member companies of the Phosgene Panel of the American Chemistry Council submit for review and public comment the Test Plan and robust summaries for phosgene (CAS 75-44-5), Cl_2CO (Fig. 1), under the U.S. Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. The purpose of this Test Plan is to summarize available physicochemical data, environmental fate and effects, and mammalian health effects data for phosgene consistent with SIDS Level 1 endpoints. Based on existing data, the Test Plan contains an analysis of the need for, and appropriateness of, testing phosgene for additional SIDS endpoints.

2.1 Methods

The scientific literature and sponsor company data on the physicochemical properties, environmental fate and effects, and mammalian toxicity endpoints for phosgene was reviewed. Searches of the TOXLINE, ECOTOX, MEDLINE, and CHEMID databases were conducted using phosgene's CAS number and chemical name. Standard handbooks and databases (*e.g.,* CRC Handbook on Chemicals, IUCLID, Merck Index, *etc*.) were consulted for physicochemical properties. Robust summaries were prepared for studies to provide details of test methods and results. Several studies may have been evaluated for a particular SIDS endpoint, but robust summaries were prepared only for the critical study that represented the best available data. Selection of the critical study was based on a review of all available studies using the ranking system developed by Klimisch *et al.* (1997), as well as the criteria outlined in EPA's methods for determining the adequacy of existing data.

2.2 Production and Use

Phosgene (Figure 1) is a highly reactive gas that is classified as a Schedule 3A toxic chemical under the Chemical Weapons Convention (CWC). While produced in Europe for use as a chemical warfare agent during WWI, the Phosgene Panel is not aware that phosgene has ever been included in the U.S. chemical weapons stockpile. Phosgene is a chemical intermediate central to the production of common commercial products and deemed essential in modern day manufacturing of products used in everyday life, such as plastics, urethanes, pharmaceuticals, agricultural chemicals and specialty chemical products.

Phosgene is produced commercially from a synthesis reaction, using chlorine and carbon monoxide. Phosgene's primary use is as a raw material for production of methylene-diphenyldiisocyanate (MDI) and toluene diisocyanate (TDI). An estimated 85% of all phosgene produced is used to make MDI and TDI, which are in turn used in the production of polyurethane. About 10% of phosgene production is used to make polycarbonate plastics. The remaining 5% is used in the production of a wide variety of pharmaceuticals, agrochemicals, and specialty chemical intermediates. Polyurethane is used in the production of foam mattresses, furniture, toys, tools, coatings, rcar bumpers and fenders. Polycarbonates are used in the production of computers, telephones, optical discs, household appliances, compact discs and cassettes.

Because of its reactive and toxic properties, industrial emissions of phosgene are strictly controlled and minimized. The majority of phosgene occurring in the troposphere is produced through thermal and photochemical decomposition of various chlorinated methane, ethane, and ethylene compounds of both natural and anthropogenic origin. The magnitude of industrial phosgene emissions is considered minor compared to indirect natural sources of the chemical in the atmosphere (Helas and Wilson, 1992).

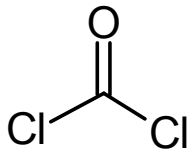

Figure 1: Phosgene

2.3 Human and Ecological Exposures

For humans, the primary route of potential exposure is by inhalation. Once inhaled, phosgene reacts with tissues of the respiratory tract to form hydrochloric acid and carbon dioxide and, therefore, only negligible amounts of inhaled phosgene are distributed in the body. Because phosgene has the potential to cause severe pulmonary irritation and, at higher doses, pulmonary edema in humans exposed by inhalation, its production is closely monitored and controlled. More than 99.9 % of phosgene produced in the U.S. is used at the facility where it is made, and is consumed in the production process. Direct industrial emissions of phosgene are minimal compared to sources from indirect photochemical reactions occurring in the troposphere (Helas and Wilson, 1992)

The boiling point of phosgene is 7.56 °C (about 40 °F). There is limited opportunity, therefore, for dermal and oral exposures to phosgene, and environmental exposures are likewise limited. Phosgene has a very short half-life (0.026 seconds) in aqueous solutions (International Programme on Chemical Safety (IPCS), 1997). Hydrolysis products of phosgene are hydrochloric acid and carbon dioxide, which are disposed of by the body through normal physiological processes. Concentrations of hydrochloric acid and carbon dioxide produced from phosgene emissions are expected to be of low ecological concern.

3.0 Test plan and Rationale

3.1 Rationale

In developing a rationale for a test plan for each SIDS Level I endpoint, data from publications and reports were evaluated for their quality using the method described by Klimisch *et al*. (1997) and professional judgment. If the reports and data were determined to be of sufficient quality, then a robust summary was prepared describing the report and data quality. In cases where data of sufficient quality to prepare a robust summary was available for a SIDS endpoint, it was concluded that no additional testing was required. For SIDS endpoints that did not have available data of sufficient quality to develop a robust summary, data from the literature were evaluated to determine if it was reasonable and technically feasible to conduct testing that would result in reproducible, defensible and meaningful data for use in hazard or risk assessments. Because of the physical and chemical properties of phosgene, it is not technically feasible to conduct certain types of tests. Attempts to conduct certain experimental studies would invariably result in inaccurate data that would not be useful in assessing the human or environmental health hazards of phosgene. The rationale for the test plan is presented in subsequent sections.

3.2 Test plan

3.2.1 Physical/Chemical Properties and Environmental Fate Studies

There are sufficient data for eight of the nine SIDS Level I physical/chemical properties and environmental fate chemistry endpoints (Table 2). Robust summaries were developed for melting point, boiling point, vapor pressure, water solubility, photodegradation, stability in water, transport between environmental compartments, and biodegradation. Secondary literature sources were used to derive values for melting point, boiling point, vapor pressure, and water solubility (IPCS, 1995). A published scientific article was used to estimate stability in water (Manogue & Pigford, 1960).

K_{ow} (partition coefficient) was the only endpoint that did not have sufficient data to support a robust summary. Although a robust summary was developed for water solubility based on an experimental study (IPCS, 1995), a water solubility value was not derived. The referenced experimental study in the robust summary demonstrated that phosgene readily reacts with water and hydrolyzes to carbon dioxide and hydrochloric acid. Phosgene was not stable in water because of its reactivity and decomposition in water. These physicochemical properties make it technically infeasible to experimentally derive a K_{ow}, therefore testing for the partition coefficient and water solubility of phosgene is not recommended. Moreover, because of rapid hydrolysis, phosgene does not persist in the environment long enough to partition into environmental compartments and, therefore, transport between environmental compartments does not apply.

Summary: Additional testing to satisfy HPV testing requirements for the physical/chemical properties and environmental fate chemistry properties of phosgene is not recommended.

Table 2: Physico-Chemical Properties/Environmental Fate Data

Data Point	Value	Reference
Melting Point	-127.8 °C	IPCS, 1995.
Boiling Point	7.56 °C	IPCS, 1995.
Vapor Pressure	1616 hPa at 20 °C	IPCS, 1995.
Water Solubility	Phosgene decomposes rapidly ($t_{1/2}$ = 0.026 sec.) in water, and therefore no accurate estimates of water solubility can be experimentally derived.	IPCS, 1995.
Photodegradation	Rates of direct and indirect photolysis of phosgene in the troposphere are negligible. The dominant process for removal of phosgene in the troposphere is hydrolytic reaction with water droplets in fog and clouds. The tropospheric hydrolysis of phosgene has been estimated over a range of latitudes, with the lifetime ranging around 10 hours, and typcially not exceeding 1 day.	Grosjean, 1991; Helas and Wilson, 1992.
Hydrolysis	Estimated half-life ($t_{1/2}$) of phosgene in water was approximately 0.026 seconds.	Manogue & Pigford, 1960
Transport Between Environmental Compartments	Fugacity modeling cannot be performed for phosgene, because of the lack of equilibrium distribution coefficients between water and other environmental media (air, soil, sediment). The transfer of phosgene vapor from air to water and soil can be derived from the aqueous- phase diffusion coefficient. This diffusion coefficient is estimated to be 1.27 x 10^{-5} cm^2/sec.	Manogue & Pigford, 1960
Biodegradation	Biodegradation is not relevant, as the material cannot co-exist with microorganisms in hydrated environmental media	Manogue & Pigford, 1960
Octanol/water partition coefficient (K_{ow})	Phosgene decomposes spontaneously in water, and therefore an equilibrium octanol/water partition coefficient cannot be derived.	IPCS, 1995.

3.2.2 Ecotoxicology

No reports or studies were found that presented data on the toxicity of phosgene to fish, aquatic invertebrates or aquatic plants. This is not surprising as phosgene is unstable and rapidly reacts with water. It is technically infeasible to conduct aquatic toxicology studies with phosgene, a

compound that hydrolyzes virtually instantaneously to form hydrochloric acid and carbon dioxide in aqueous solutions (phosgene half-life in aqueous solutions is estimated to be 0.026 seconds – Manogue & Pigford, 1960). Therefore, it is not technically feasible to conduct EPA or OECD guideline studies because of the reactive nature of phosgene in water.

For industrial use, phosgene is primarily both made and used in closed systems, and the material presents minimal probability of exposure to aquatic environments. In the unlikely event that phosgene is emitted directly to water, any associated effects on aquatic organisms will be attributed to formation of hydrochloric acid and an associated drop in pH. The acute ecological effects of hydrochloric acid have been extensively studied, and are reported in a separate IUCLID dataset. Therefore, additional studies on the ecotoxicity of phosgene are neither feasible nor proposed.

Summary: Additional testing to satisfy HPV testing requirements for ecotoxicity properties of phosgene is not recommended.

3.2.3 Mammalian Toxicology

The physical and chemical properties of phosgene, to a large measure, dictate the site and nature of health effects observed. Phosgene is expected to react rapidly with water to form carbon dioxide and hydrochloric acid. It also reacts with macromolecules containing sulfhydryl, amine and hydroxyl groups in aqueous solutions (Babad and Zeiler, 1973). Phosgene is a gas under ambient conditions, therefore the primary route of potential human exposure is inhalation. Thus, the most relevant route of exposure for toxicity testing is via inhalation. The primary toxic effects in response to both acute and repeated exposures to phosgene are focused on the portal of entry, the respiratory tract. Acute inhalation toxicity studies conclude that, at lethal concentrations, the most common findings are non-cardiogenic pulmonary edema (Frosolono and Pawlowski, 1977; Pawlowski and Frosolono, 1977; Diller *et al*., 1985) and effects on pulmonary function (Sciuto *et al*., 2002). However, the exact mechanism of phosgene toxicity is not clearly defined.

In considering whether to perform additional studies to evaluate systemic organ toxicity of phosgene, the technical feasibility of conducting studies to evaluate specific endpoints and the likelihood of acquiring useful information must be taken into account. As is characteristic of many highly reactive vapors, the portal-of-entry effects of phosgene following repeated sublethal concentrations are well documented (Kodavanti *et al*., 1997). Phosgene's physical/chemical properties mitigate against the likelihood of systemic effects. To produce adverse effects on systemic organ systems, there must be sufficient time for phosgene to traverse the aqueous surfactant layer of the lungs, the epithelial tissue, interstitium and the endothelium of pulmonary capillaries. Any unreacted phosgene entering the pulmonary capillary circulation must then be transported to the various organ systems distal to the lungs. The half-life of hydrolysis for phosgene has been experimentally determined to be 0.026 seconds and the resultant hydrolysis products are carbon dioxide and hydrochloric acid (Manogue and Pigford, 1960). Nash and Prattle (1971) have shown that the diffusion path length of phosgene in an aqueous solution is approximately 8 μm. This length is greater than the distance from the alveolar airspace to the

interior of the pulmonary capillary (about 1 μm). Thus, in a uniform aqueous medium phosgene is deemed able to diffuse across a distance sufficient to transit the gas-blood barrier.

Using a conservative assumption that the composition of surfactant and cellular constituents do not impose a greater physical impediment to diffusion of phosgene compared to a homogeneous aqueous environment, phosgene can potentially enter the blood stream following inhalation exposure. Consistent with this assumption, Sciuto *et al*. (1996) have shown that if the exposure concentration is sufficiently high, phosgene interactions with blood can be demonstrated. Any phosgene entering the systemic circulation within the lungs is still prone to rapid hydrolysis in this aqueous environment.

To examine the potential for phosgene to reach a systemic organ system unaltered, the blood circulation time in an adult rat was calculated for comparison to the half-life of phosgene. The mean measured cardiac output was 131 ml/min for a group of rats with a mean weight of 366 g (Delp *et al*., 1991). Total blood volume was estimated to be 27.08 ml for a rat with a body weight of 366 g (Brown *et al*., 1997). Using the values for total blood volume and cardiac output, circulation time in a 366 g rat is calculated to be approximately 12.4 seconds. As a first approximation, the time for phosgene to transit from the pulmonary capillaries to the heart is taken to account for 25% of the total circulation time or approximately 3.1 seconds. This time is consistent with measurements of mean transit time between the heart and the foot (approximating 25% of the complete circulation circuit) of rats with a mean weight of 340 g that was slightly greater than 3 seconds (Ishizuka, 1988). Comparing a nominal transit time from the lung capillaries to the first systemic organ (heart) of 3.1 seconds to the half-life of phosgene in an aqueous solution (0.026 sec), the transit time is equivalent to approximately 119 half-life periods of phosgene. Thus, it is not likely that phosgene absorbed by the pulmonary capillaries will reach the heart. By extension of this logic, it becomes even more remote that phosgene could reach organ systems distal to the heart such as reproductive organs (transit time is greater than 200 half-lives) and constitute a cause of concern for reproductive or developmental toxicity. The hydrolysis of phosgene is expected to lead to carbon dioxide and hydrochloric acid. The carbon dioxide will be exhaled and the buffering capacity of blood is far in excess of that required to neutralize the hydrochloric acid resulting from inhalation exposure of humans to dangerous concentrations of phosgene (Nash and Prattle, 1971).

The propensity of phosgene to induce lung damage consequently leads to secondary hypoxia, hypercapnia and acidosis following inhalation (Sciuto *et al.*, 2001). These changes in blood may influence developmental and reproductive parameters but are indirect sequelae to direct damage by phosgene of lung tissue. Thus, using animals for new studies in which exposures are at air concentrations that result in such secondary effects is not warranted in that these effects are not unique to phosgene.

In reviewing the existing database of toxicity studies for phosgene, it is concluded that there exists adequate toxicity testing of phosgene for purposes of HPV Program hazard assessment.

Three acute inhalation toxicity studies, one an OECD 403 guideline study in rats and mice, are available for the acute toxicity endpoint (Zwart *et al.*, 1990; Arts *et al.*, 1989). Thirty-minute LC_{50} values were 21 ppm in rats and 5-19 ppm in mice.

Adequate repeat dose toxicity studies, which provide sufficient data to assess repeat dose hazard from phosgene exposure, are available as well. A 12-week inhalation exposure study in rats indicates that a concentration of 0.1 ppm for 6 hrs/day, 5 days/week can be tolerated without lethality, but with some histopathologic effects in the lung (Kodavanti *et al.*, 1997). In comparison, in a 2-week repeat inhalation study in rats, there were no histopathologic effects on a wide array of systemic tissues at a phosgene exposure of 1.0 ppm for 4 hrs/day, 5 days/week (DuPont Chemical Solutions Enterprise, 1976a & b).

An OECD guideline *in vitro* genetic toxicity study of phosgene (Reichert *et al*., 1983) was considered negative, though phosgene could only be detected in the test system at cytotoxic concentrations of >10,000 ppm (*i.e.,* phosgene reacted with test system constituents at lower concentrations).

There are no reproductive, developmental, or *in vivo* genetic toxicity studies available for phosgene. However, since inhaled phosgene would react with lung tissue and macromolecules in blood, or, as discussed above, be hydrolyzed before it could even reach other relevant systemic sites or target organs ($t_{1/2}$ = 0.026 seconds, Manogue & Pigford, 1960), conducting new studies to evaluate toxicity to systemic organ systems is not expected to yield useful information and is considered both an injudicious use of experimental animals and a misallocation of other resources.

Because of the propensity for phosgene to produce portal-of-entry effects, it is likely that other systemic organ systems or tissues would be affected only at exposure concentrations that produce lung toxicity. Thus, any observed systemic effects may be secondary to direct effects on the respiratory tract.

3.2.3.1 Acute Toxicity

Acute toxicity of phosgene has been adequately evaluated in rats and mice (Zwart *et al.*, 1990; Arts *et al.*, 1989). Acute LC_{50} values for rats resulting from three different exposure durations were: 10 min = 334 mg/m^3 (83.5 ppm); 30 min = 84 mg/m^3 (21 ppm); 60 min = 49 mg/m^3 (12.25 ppm). Acute LC_{50} values for mice were generally comparable.

3.2.3.2 Genetic Toxicity

Phosgene was reported to be negative under the conditions of the Ames bacterial mutagenicity assay (liquid incubation assay with and without metabolic activation) (Reichert *et al.*, 1983). Although no specific detailed data for phosgene test results were reported, the authors concluded that the negative result was likely due to phosgene reacting rapidly in the test medium. This was verified by gas chromatographic analysis. Additional *in vitro* testing would be subject to similar technical limitations imposed by the water reactivity of phosgene, and is not proposed. As discussed above, the physical and chemical properties of phosgene precludes a valid *in vivo* test of genetic toxicity by standard procedures.

Table 3: Health Effects Data – Acute & Genotoxicity Data

Data Point	Value		Reference
Acute Oral (LD_{50}, mg/kg)	-		-
Acute Dermal (LD_{50}, mg/kg)	-		-
Acute Inhalation (LC_{50}, mg/m^3)	10 min. exp.:	334 mg/m^3 (rats) 244 mg/m^3 (fem. mice) 322 mg/m^3 (male mice)	Zwart *et al.*, 1990 Arts *et al.*, 1989
	30 min. exp.:	84 mg/m^3 (rats) 47 mg/m^3 (fem. mice) 76 mg/m^3 (male mice)	
	60 min. exp.:	49 mg/m^3 (rats) 21 mg/m^3 (fem. mice) 39 mg/m^3 (male mice)	
Genotoxicity - *In Vivo*	-		-
Genotoxicity – *In Vitro*	Phosgene is non-mutagenic under the conditions of the *S. typhimurium* test system, because it reacts rapidly in the test medium.		Reichert *et al.*, 1983

3.2.3.3 Repeat Dose Toxicity

Toxic effects of repeated exposure to phosgene have been evaluated in two complementary inhalation exposure studies. The more recent study by Kodavanti *et al*. (1997) focused on pulmonary effects. Separate groups were exposed 6 hours per day, 5 days per week as air controls or to analytically determined concentrations of 0.1 or 0.2 ppm phosgene for 4 or 12 weeks. In addition, other groups of rats were exposed for 2 days per week to 0.5 ppm or for 1 day per week to 1.0 ppm for 4 or 12 weeks. This extensive study design allowed investigation of the interaction of concentration and time of exposure. The endpoints measured were body and lung weights, lung displacement volume, histopathology of the lungs and indices of changes in lung collagen. This investigation provides a detailed description of the progression and severity of lung effects of phosgene. The focused nature of the Kodavanti *et al*. (1997) study is supplemented by an earlier study (DuPont Chemical Solutions Enterprise, 1976a & b) in which rats were exposed as air controls or to analytically determined concentrations of 0.2 or 1.0 ppm phosgene 4 hours per day, 5 days per week for two weeks. Body weights, clinical signs of toxicity, organ weights (lungs, heart, liver, kidneys, testes, spleen, thymus) and histopathology (trachea, lungs, heart, liver, kidneys, testes, epididymides, lymph nodes, spleen, thymus, sternum

(including bone marrow), thyroids, parathyroids, adrenals, pancreas, esophagus, stomach, intestine, eyes, brain and skin). No compound-related effects were observed. A direct comparison of groups exposed to, for example, the same concentration of 1.0 ppm is not reasonable because of variances in length of daily exposure, number of exposures per week and total duration of exposure. This may account for the observation of pulmonary lesions in the study by Kodavanti *et al.* (1997) and not in the earlier study (DuPont Chemical Solutions Enterprise, 1976a & b). Nevertheless, these studies confirm the findings of acute studies in that the pulmonary system is shown to be the target organ of repeated exposure phosgene toxicity and constitute a detailed investigation of the severity and progression of lesions in the target organ following repeated exposures to phosgene.

Table 4: Health Effects Data – Repeated Dose, Reproductive & Developmental Toxicity

Data Point	Value	Reference
Repeated Dose Toxicity	LOAEL = 0.1 ppm (inhalation, 12 weeks, rats)	Kodavanti *et al.*, 1997
	NOAEL > 1.0 ppm (2 weeks, inhalation, rats)	Dupont Chemical Solutions Enterprise, 1976a & b
Reproductive Toxicity	-	-
Developmental Toxicity	-	-

3.2.3.4 Reproductive and Developmental Toxicity

There are no reproductive or developmental toxicity studies of phosgene available. However, as inhaled phosgene is expected to react with lung tissues and macromolecules in blood or, alternatively, to be hydrolyzed before it could even reach relevant systemic sites or target organs, such studies would not be expected to provide a valid test for reproductive or developmental parameters. World Health Organization scientists, in the IPCS (1997) review of phosgene, concluded that "*the very short half-life (0.026 seconds) in aqueous solutions preclude a significant retention of phosgene in the body.*" In addition, since the lung appears to be the critical target organ, it is also considered likely that other systemic organ systems or tissues would be affected only at exposure concentrations that produce sufficient lung toxicity to invalidate interpretation of test results. In fact, in the 2-week repeat inhalation study cited above, male reproductive organs were not affected following phosgene inhalation. The propensity of phosgene to cause lung effects consequently led to secondary effects such as hypoxia that could influence developmental endpoints.

Summary: For purposes of satisfying HPV toxicity testing requirements for hazard assessment, it is concluded that no additional toxicity testing for the SIDS level I endpoints is necessary.

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